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Does *Chrysophyllum albidum* Fruit (Cherry) Induce Abortion/Miscarriage or Not

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Authors' contributions

This work was carried out in collaboration with all authors. Author AIA conceptualized and designed the study and also wrote the manuscript. Author EOO managed the analyses of the study. Authors VNO and JAE managed the literature searches. Author UO wrote the protocol. Author EOA performed the statistical analysis. All authors read and approved the final manuscript.

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ABSTRACT

Background: There is a general belief that *Chrysophyllum albidum* fruit (cherry) has the ability to induce abortion (miscarriage) in pregnant women due to its sour taste.
Aim: This study sought to investigate if this fruit actually induces miscarriage or not.
Methods: Freshly harvested *C. albidum* fruits were purchased from a local market in Orita-Challenge Area of Ibadan. The seeds were removed and the juice was extracted. Thirty fertile male and thirty female Wistar rats were used for this study. After seven days acclimatization, the female rats were separated into its individual cages and had estrus synchronization using Diethylstilbestrol dissolved in paraffin oil and administered at the dose of 1 mg/kg body weight. A male was then introduced into each cage for mating. On the 7th day vaginal smear of each of the female rats was made on a clean glass slide by carefully inserting a cotton-tipped swab moistened with normal saline into the vaginal cavity of the rats and rolled gently against the wall before

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withdrawal. The smear was stained with Giemsa and observed under microscope to check for presence of protein coagulates. After confirmation of pregnancy, the pregnant rats were grouped into four. Group A was treated with normal saline, groups B, C and D were treated with undiluted *C. albidum* fruit juice for 24, 48 and 72 hours respectively. The animals were then observed daily till they littered. *In vitro* effect of the fruit on isolated rat uteri was determined using standard method.

Results: No abortion was observed all through the period of pregnancy following administration of *C. albidum* fruit juice as all the pregnant rats appeared physically healthy and successfully littered at the end of pregnancy.

Conclusion: *C. albidum* fruit induced multiple contractions of the pregnant rat uteri following *in vitro* administrations but did not induce abortion when administered to pregnant rats. This suggests that cherry fruit contains active agents which could be isolated and processed into pure utero-tonic agents for use by routes other than the oral. Hence, the consumption of cherry remains relatively safe in pregnancy.

Keywords: Chrysophyllum albidum; pregnancy; abortion/miscarriage; oxytocin; uterus contraction.

1. INTRODUCTION

Chrysophyllum albidum (Linn.) also called African star apple belongs to the family Sapotaceae. It is primarily a forest tree species and its natural occurrences have been reported in diverse ecozones in Nigeria, Uganda, Niger Republic, Cameroon and Cote d'Ivoire [1]. The plant often grows to a height of 36.5m though it may be smaller [1]. In Nigeria, it is commonly referred to as cherry, Agbalumo by the Yorubas and Udala by the Ibos. The African star apple fruit is a large berry containing 4 to 5 flattened seeds or sometimes fewer due to seed abortion [2]. The plant has in recent times become a crop of commercial value in Nigeria. The fleshy pulp of the fruits is eaten especially as snack and relished by both young and old [3]. The African star apple fruit has been found to have highest content of ascorbic acid with 1000 to 3,330 mg of ascorbic acid per 100gm of edible fruit or about 100 times that of oranges and 10 times of that of guava or cashew [4]. It is reported as an excellent source of vitamins, irons, flavours to diets and raw materials to some manufacturing industries [5,6,7]. In addition, its seeds are a source of oil, which is used for diverse purposes. The seeds are also used for local games [1]. The fruits also contain 90% anacardic acid, which is used industrially in protecting wood and as source of resin, while several other components of the tree including the roots and leaves are used for medicinal purposes [1,8].

C. albidum fruit is common in both urban and rural center especially during the months of December to April. The fruits are not usually harvested from the trees, but left drop naturally to the forest floor where they are picked. Allowing the fruits to drop before picking promotes fungal infections. Recent market survey revealed that the fruits often deteriorate within a very short period. There is a dearth of information on the pharmacological benefits of *C. albidum* fruit. Due to its sour taste, there is a general belief that it has the ability to induce abortion (miscarriage) in pregnant women. This study sought to investigate if this fruit actually induce miscarriage or not.

Oxytocin is a nine amino acid peptide hormone secreted by the posterior pituitary that elicits milk ejection in female animals and women. In pharmacological doses, oxytocin can be used to induce uterine contraction and maintain lactation [9,10].

Oxytocin and vasopressin are typical neural hormones. The binding protein for oxytocin is designated neurophysin I and that for vasopressin is designated neurophysin II. Both neurophysins are similar in structure. The hormone-neurophysin complex stabilizes the hormone within the neurosecretary granules. Oxytocin is stored as neurosecretary granules and released from axonal terminals by calcium-dependent exocytosis [11,12]. In fact oxytocin has been best known for its roles in female reproduction. It is released in large quantities during labor, and after stimulation of the nipples. It is a facilitator for childbirth and breastfeeding. However, recent studies have begun to investigate oxytocin role in various behaviors, including orgasm, social recognition, bonding, and maternal behaviors. oxytocin is believed to be involved in a wide variety of physiological and pathological functions such as sexual activity, penile erection, ejaculation, pregnancy, uterine

contraction, milk ejection, maternal behavior, social bonding, stress and probably many more [13].

Oxytocin is usually administered intravenously to induce contractions during parturition. It is also available as nasal spray to induce lactation post-partum. Oxytocin infusion near term will produce contractions that decrease the fetal blood supply. It is inactive orally because it is destroyed by gastric and intestinal enzymes [9].

Oxytocin is also used to stop bleeding postpartum. For this purpose, it is given intravenously or intramuscularly. It is released into the bloodstream as a hormone in response to stretching of the cervix and uterus during parturition and with stimulation of the nipples during lactation [14]. In estrogen and progesterone primed rodents, injections of prolactin cause the formation of milk droplets and their secretion into the ducts but oxytocin causes contraction of the myoepithelial cells lining the duct walls which results in ejection of milk through the nipple. Membrane receptors for oxytocin are found in both uterine and mammary tissues. These receptors are increased in number by estrogens and decreased by progesterone. The concomitant rise in estrogen and fall in progesterone occurring immediately before parturition probably explains the onset of lactation in some individuals prior to delivery [11,15]. The primer for commencement of parturition in humans is secretion of oxytocin by certain cells of the fetus. The oxytocins secreted in turn activate some cells of the placenta to produce and release prostaglandins. Oxytocin and prostaglandins synergize to stimulate the uterine myometria leading to more vigorous and more frequent contractions. At this point, the increasing emotional and physical stresses caused by these contractions activate the mother‟s hypothalamus which signals for oxytocin release by the posterior pituitary. The elevated levels of oxytocin and prostaglandins trigger the rhythmic expulsive contraction of true labour [16].

2. METHODOLOGY

2.1 Collection and Extraction of Plant Materials

Freshly harvested *C. albidum* fruits were purchased from a local market in Orita-Challenge Area of Ibadan, Nigeria in February 2018. The fruits were washed thoroughly with clean water and were cut into two. The back and seeds were removed and the juice was extracted using an electronic juicer. The resulting juice was poured in a sterile bottle and stored in the refrigerator for further analysis.

Fig. 1. *Chrysophyllum albidum* fruits [5]

2.2 Experimental Design and Animal Treatment

Thirty fertile male and thirty virgin female Wistar rats weighing between 170 and 200 g were purchased from the Central Animal House, College of Medicine, University of Ibadan, Nigeria. They were acclimatized for seven (7) days during which they were fed *ad libitum* with standard feed and drinking water and were housed in clean cages placed in well-ventilated housing conditions (under humid tropical conditions) throughout the experiment. All the animals received humane care according to the criteria outlined in the 'Guide for the Care and Use of Laboratory Animals' prepared by the National Academy of Science and published by the National Institute of Health. After the acclimatization period, the female rats were separated into its individual cages and had estrus synchronization using Diethylstilbestrol dissolved in paraffin oil and administered at the dose of 1 mg/kg body weight. A male was then introduced into each cage for mating. On the 7^{th} day vaginal smear of each of the female rats was made on a clean glass slide by carefully inserting a cotton-tipped swab moistened with normal saline into the vaginal cavity of the rats and rolled gently against the wall before withdrawal. The smear was stained with Giemsa and observed under microscope to check for presence of protein coagulates. After confirmation of pregnancy, the pregnant rats were grouped into four in the following order:

Group A: Normal saline *ad libitum* (control).

Group B: Undiluted *C. albidum* fruit juice *ad libitum* for 24 hours.

Group C: Undiluted *C. albidum* fruit juice *ad libitum* for 48 hours.

Group D: Undiluted *C. albidum* fruit juice *ad libitum* for 72 hours.

The 24, 48 and 72 hours were chosen to evaluate the daily differences. The animals were then observed daily till they littered.

2.3 *In vitro* Effect of *C. albidum* Fruit Juice on Isolated Rat Uteri

The method described by Nwankudu et al. [17] was adopted: Briefly matured pregnant female rats were sacrificed by stunning and decapitation. The lower abdomen was opened and the two uterine horns were harvested and transferred into De Jalon solution that continuously bubbled with air and maintained at 37°C (pH 7.4). The De Jalon solution was constituted such that each liter contained: NaCl (9 g), KCl (0.42 g), $CaCl_2$ (0.06 g), $NaHCO_3$ (0.5 g), and glucose (0.5 g). Each uterine horn was suspended vertically in a 35 mL organ bath by means of ligatures attached at one end to a tissue holder and at the other end to an isometric force displacement transducer connected to a digital physiological recorder (Medicaid Physiopac) for displaying isometric contractions. Resting tension in the muscle strip was readjusted, just sufficient to remove the slack. The preparation was allowed to equilibrate within 30 minutes of mounting. After recording regular rhythmic contractions, dose-response relationships were established for *C. albidum* fruit juice and other standard drugs used. For all administrations, a minimum time of 1 minute was allowed for individual tissue responses before being washed 3 times with De Jalon solution. The test substances were administered as final bath concentration (FBC).

Percentage (%) rise in Amplitude of Contraction was calculated as:

Percentage (%) rise in Amplitude of Contraction

$$= \frac{\text{Amplitude of Contraction with C.albidum fruit juice} - \text{Basal Amplitude of Contraction}}{\text{Amplitude of Contraction with C.albidum fruit juice (mm)}} \times 100$$

2.4 Statistical Analysis

Data were subjected to analysis of variance using Graph Pad Prism. Results were presented as Mean ± standard deviation. One way analysis of variance (ANOVA) was used for comparison of the means followed by Tukey's (HSD) multiple comparison test. Differences between means were considered to be significant at $p<0.05$.

3. RESULTS AND DISCUSSION

No abortion was observed throughout the period of pregnancy following *C. albidum* fruit juice administration as all the pregnant rats appeared physically healthy and successfully littered at the end of pregnancy. There was no difference between the control group and all test groups (Table 1).

All doses of cherry juice administered significantly induced contractions of the isolated rat uteri ($p<0.05$) with 0.05, 0.1, 0.2. 0.3 and 0.4

raised the amplitudes of contractions from 5 mm to 17.45 ± 1.48, 24.11 ± 1.86, 25.00 ± 1.96, 27.12 ± 1.62 and 28.08 ± 1.38 respectively. The contractions induced by cherry compared favourably with that of the standard agent oxytocin.

In Table 1, all the pregnant rats in group A (control) treated with normal saline throughout the experiment littered. In group B, undiluted cherry juice was given for 24 hours, and at the end of the experiment, all littered. In group C, undiluted cherry juice was given to the pregnant rats for 48 hours and they all littered as well. In group D, the pregnant rats were given undiluted cherry juice for 72 hours and they all littered at the end of the experiment. This is similar to the report of Nwankudu et al. [17] who treated animals with pineapple juice for 24, 36, and 48 hours respectively.

Table 1. *In vivo* activity of fresh *C. albidum* Fruit (Cherry) juice on Pregnant Rats' Uteri

Treatment groups	Pregnancy test	Type of treatment	Number that littered	Percentage (%) that littered
A	Positive	Normal Saline	5	100
B	Positive	Undiluted *C. albidum* fruit juice ad libitum for 24 hours	5	100
C	Positive	Undiluted *C. albidum* fruit juice ad libitum for 48 hours	5	100
D	Positive	Undiluted *C. albidum* fruit juice ad libitum for 72 hours	5	100

Table 2. *In vitro* effect of *C. albidum* fruit (Cherry) Juice on isolated Pregnant Rats' Uteri

Volume Administered (ml)	Basal Amplitude of Contraction (mm)	Amplitude of Contraction with *C. albidum* fruit juice (mm)	Percentage (%) rise in Amplitude of Contraction
0.05	5.00	17.45 ± 1.48	249
0.10	5.00	24.11 ± 1.86	382.2
0.20	5.00	25.00 ± 1.96	400
0.30	5.00	27.12 ± 1.62	442.4
0.40	5.00	28.08 ± 1.38	461.6

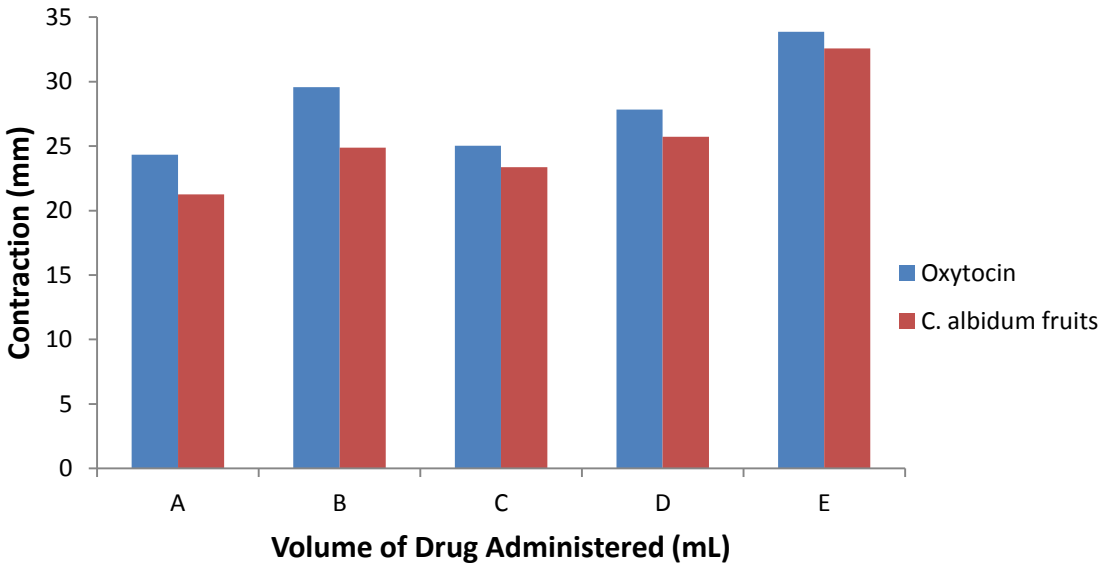

Fig. 2. Comparative effects of oxytocin and *C. albidum* fruit (Cherry) juice on an isolated pregnant rat uterus

In the *in vitro* experiment, cherry juice elicited a dose dependent multiple contractions of the pregnant rat's uterus. These effect was significantly different ($p<0.05$) from the basal contractions, with 0.40 ml of juice eliciting the highest increase in amplitude of 461.6% (Table 2). The effect of cherry juice on an isolated pregnant rat uterus compared with that of a standard utero-tonic agent oxytocin showed that Oxytocin was giving slightly higher effect than cherry juice at all doses (Fig. 2). This contradicts the study of Nwankudu et al. [17] who reported greater effect for Oxytocin only at lower doses when animals were treated with pineapple juice. cherry juice when administered to the isolated pregnant rat uteri induced multiple uterine contractions in a manner similar to that of Oxytocin. This result suggests that cherry juice may contain bioactive principles capable of inducing uterine contractions and as such could be used to facilitate labor or as an abortificient. This might be due to the ability of cherry to bind to histaminergic (H_2) receptors present in the rat uterus [18], promoting calcium flux in the smooth muscles [19].

In the *in vivo* work, the contractile effect of cherry juice was not observed as all pregnant rats given oral cherry juice littered at full term with no abortion induced. This result suggest that the active component(s) of the juice that has the uterine contractile effect may have been affected and transformed by digestive enzymes, thereby causing the juice to lose its utero tonic property when taken orally.

4. CONCLUSION

Cherry juice induced multiple contractions of the pregnant rat uteri following *in vitro* administrations but did not induce abortion when administered to pregnant rats. This suggests that cherry contains active agents which could be isolated and processed into pure utero-tonic agents for use by routes other than the oral. Hence, the consumption of cherry remains relatively safe in pregnancy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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